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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-92* is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner and Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michael Szperka, Art Unit 1644.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 11, 2005 has been entered.

Claims 82-92 are pending in the instant application.

3. Applicant's arguments, see pages 4 and 5 of the response filed August 13, 2004 and page 4 of the response filed March 11, 2005, with respect to the rejection of claims 82-92 under 35 USC 112 have been fully considered and are persuasive. The prior rejection of claims 82-92 under 35 USC 112, first paragraph for lack of enablement has been withdrawn.

4. Applicant has successfully overcome all rejections set forth in prior office actions. However, examination of the claims has uncovered new grounds of rejection.

Claim Objections

5. Claim 90 is objected to because of the following informalities: The term interleukin is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 82-92 are rejected under 35 U.S.C. 102(e) as being anticipated by Gorman et al. (US Patent No. 6,242,586, of record as reference B on form 892 dated March 27, 2003, see entire document).

Gorman et al. teach antibodies to a mouse protein designated 499E9 (see entire document, particularly Example 5). These antibodies can be polyclonal or monoclonal, with it being taught that desirable monoclonal antibodies are to be prepared from human hosts (see particularly Example 5 and column 15, lines 65-67). The antibodies of

Gorman et al. are also taught as being modified to produce chimeric, humanized and recombinant forms (see particularly column 16, lines 10-33). As such, Gorman et al. teach the production of human monoclonal antibodies to 499E9, and these teachings are fully supported by their disclosure in US provisional application 60/032,846, filed December 13, 1996. 499E9 is the same protein as mouse osteoprotegerin binding protein (see the office action mailed March 27, 2003, pages 8 and 9), and human osteoprotegerin binding protein (SEQ ID NO:39) is 84.1% identical to the 499E9 protein disclosed by Gorman et al. (see enclosed copy of sequence search notes).

The instant claims recite the functional limitation that the claimed human monoclonal antibodies inhibit osteoclast formation. It is noted that the disclosure of Gorman et al. do not teach the 499E9 protein as being involved in bone remodeling processes. However, given that the sequences of human and mouse osteoprotegerin binding proteins are substantially identical, it is reasonable that antibodies that specifically bind mouse osteoprotegerin binding protein as taught by Gorman et al. will also bind human osteoprotegerin binding protein. It is also reasonable that these same antibodies that cross-react with human osteoprotegerin binding protein will inhibit osteoclast formation, especially in the absence of evidence to the contrary. Applicant's specification does not appear to clearly indicate the region or regions of human osteoprotegerin binding protein that must be bound by an antibody to ensure an inhibition of osteoclast formation. As such, even though Gorman et al. do not teach the functional limitation of inhibiting osteoclast formation, the structure of the antibodies taught by Gorman et al. are substantially identical to those recited in the instant claims.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 82, 83, and 85-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popoff et al. (US Patent No. 5,641,747, see entire document) as evidenced by Yang et al (PNAS (1985) 82:7994-7998, see entire document), in view of Lonberg et al. (WO 93/12227, see entire document, of record as reference BC on the IDS received March 25, 1999).

Popoff et al. teach that antibodies that bind to, and block the activity of, activated vitamin D-binding factor (DBP-MAF) can be used to prevent osteoclast function and bone resorption (see entire document, particularly the abstract, column 3 lines 22-37, and column 4, lines 48-67). These antibodies can be polyclonal, monoclonal, chimeric, or humanized, with either human chimeric antibodies or humanized antibodies being preferred for treatment of diseases such as rheumatoid arthritis and osteoporosis (see particularly from line 26 of column 12 to line 23 of column 14, column 8, lines 52-67 and column 9, lines 1-25). The sequence of DBP-MAF was well known in the art at the time of the invention of Popoff et al. (see particularly column 5, lines 12-26 and the entirety of Yang et al., PNAS (1985) 82:7994-7998, especially Figures 1 and 2). Popoff et al. demonstrated that rats that are genetically deficient in their ability to make DBP-MAF have reduced numbers of osteoclasts, and this phenotype can be reversed by the administration of DBP-MAF (see particularly from line 46 of column 6 to line 13 of column 7). As such, administration of an antibody that binds to, and blocks the activity of, DBP-MAF would reduce the number of osteoclasts by inhibiting their formation.

It is noted that the claims are drawn to a human monoclonal antibody that binds an epitope, wherein the epitope comprises **at least a part** of SEQ ID NO:39 (human osteoprotegerin binding protein). The phrase "at least a part of" does not appear to be clearly defined by the specification. As such, it is not clear to the examiner that the epitope recognized by the claimed antibody is 100% contained within SEQ ID NO:39. It is reasonable that an epitope that has at least one amino acid in common with SEQ ID NO:39 comprises **at least a part** of SEQ ID NO:39. The DBP-MAF protein contains

many amino acids in common with SEQ ID NO;39, and therefore the antibodies disclosed by Popoff et al. meet the limitation of binding an epitope that comprises **at least a part** of SEQ ID NO:39.

Popoff et al. do not teach that their antibodies are human antibodies.

Lonberg et al. teach the use of transgenic mice that contain human immunoglobulin heavy and light chains to make human antibodies (see entire document, particularly the abstract). Human antibodies offer an advantage over all other antibody type for *in vivo* diagnostic and therapeutic use in that the use of human antibodies reduces anti-therapeutic antibody responses, including HAMA responses (see particularly page 1, lines 27-38). Such responses are generated due to the inherent immunogenicity of non-human immunoglobulins. When non-human antibodies are administered to a human patient, the patient's immune system produces antibodies that neutralize the efficacy of the therapeutic antibodies, and the resulting antibody complexes can also cause acute toxicity (see particularly page 1, lines 27-38). Human antibodies would not be highly immunogenic in human patients, and as such unwanted anti-antibody responses could be reduced (see particularly page 1, lines 27-38).

Therefore, a person of ordinary skill in the art would have been motivated to make the therapeutic antibodies designed for human administration of Popoff et al. using the methods and teachings of Lonberg et al. so that the resulting product would be a human monoclonal antibody. Motivation to do this comes from the teachings of Popoff et al. that the antibodies are to be administered to human patients and the teachings of Lonberg et al. that human antibodies are the most preferred type of

antibody for *in vivo* use since they have very low immunogenicity that does not elicit unwanted anti-therapeutic antibody responses in the patient.

As noted above, the phrase "comprising at least a part of" has been interpreted such that the epitope recognized by the claimed human monoclonal antibody need only recognize a single amino acid found within SEQ ID NO:39, this single amino acid being located in the context of other sequence that can be unrelated to SEQ ID NO:39. Appropriate amendment of the claim to limit epitopes to those found completely within SEQ ID NO:39 would remove this rejection.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 82-92 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-9, 21, and 22 of copending Application No. 10/180,648. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/180,648 anticipate the instant invention. Specifically, the claims of '648 are drawn to a fully human monoclonal antibodies and compositions comprising antibodies wherein the antibodies have specifically defined heavy and light chain variable regions that inhibits the binding of human osteoprotegerin binding protein (also known as OPGL and RANKL) to an osteoclast differentiation and activation receptor (see also Examples 1-9 of '648, especially paragraph 234 on page 96). Monoclonal antibodies have a single, defined binding specificity, and the regions of the antibody molecule responsible for specifically binding the target antigen are the variable regions. Since the claims of '648 recite specific variable region sequences, they are monoclonal antibodies and thus anticipate the claimed genus of human monoclonal antibodies that bind human osteoprotegerin binding protein. Note that single chain Fv antibodies do not naturally occur, and as such they must be made recombinantly using molecular biology techniques.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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